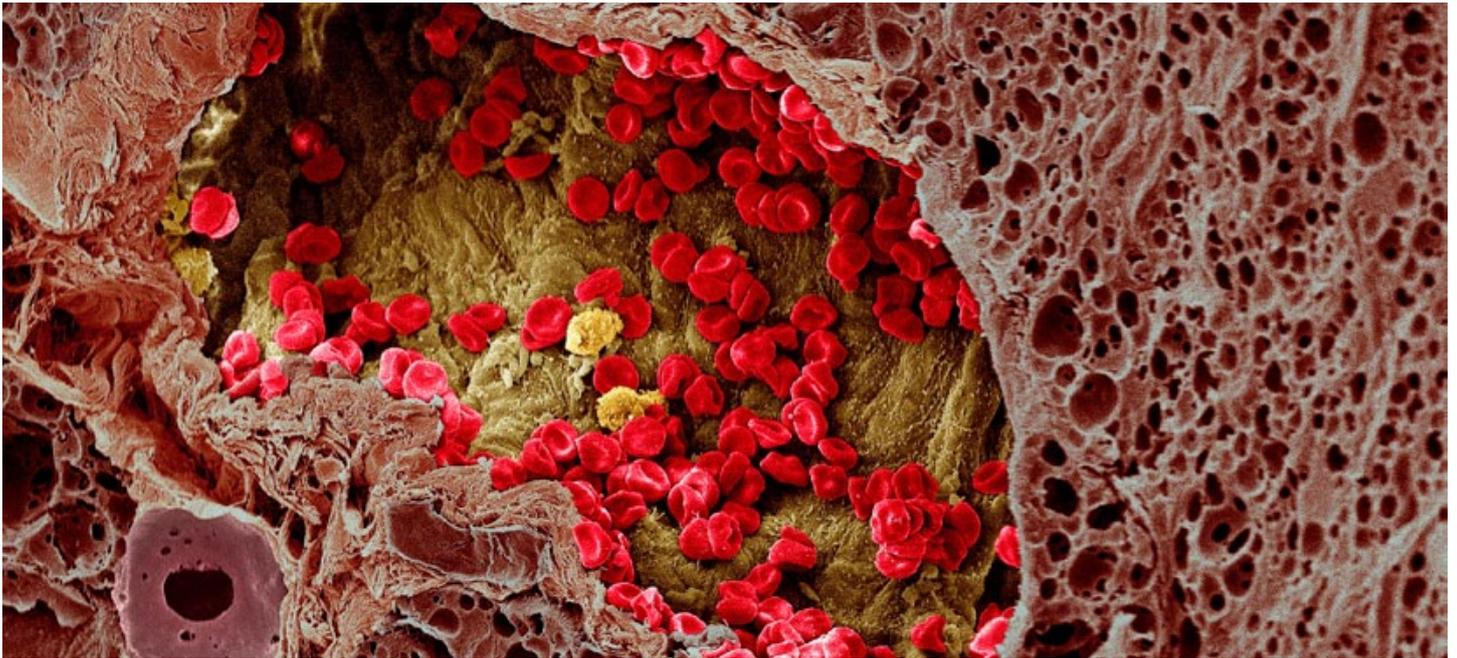


Novel orally bioavailable BRAF inhibitors for the treatment of malignant melanoma and other cancers



SEM of blood vessel in a melanoma. K Hodivala-Dilke & M Stone/Wellcome Images

Opportunity

The incidence of melanoma is rising faster than that of any other solid tumour. Almost a third of cases occur in those under 50 years old, with melanoma being the second most common cancer in the 15–34 age group. In malignant melanoma (advanced melanoma), the median survival for fit patients is 6–9 months. Despite recent therapeutic advances for the systemic treatment of malignant melanoma, there are still commercial opportunities for the remaining unmet needs.

BRAF is an intracellular protein kinase that is a validated drug target for the treatment of malignant melanoma and other cancers. Through a comprehensive drug discovery programme, the Institute of Cancer Research has identified two novel orally bioavailable preclinical candidates that target BRAF and are suitable for further development. These candidates have a different profile from the current therapy for malignant melanoma, offering a broader therapeutic profile.

The Wellcome Trust, in conjunction with the Royal Marsden and the Institute of Cancer Research, is supporting IND enabling studies, regulatory filing and a subsequent adaptive (and expansion) phase I trial of these candidates. The Trust is seeking a commercial partner on this exciting programme to undertake commercial development and bring a product to the clinic.

Unmet need

Even with the recent major therapeutic advances for the treatment of malignant melanoma, there remains a significant unmet need. Progression-free survival remains limited (~7 months) and acquired resistance, as with all targeted therapeutic agents, appears inevitable. In addition to these factors, some patients have BRAF mutant tumours that are intrinsically resistant to the existing therapies and in ~30% of cases patients treated with current therapies develop non-melanoma skin lesions. Furthermore, the current therapy should not be prescribed for melanoma patients with RAS mutant tumours (~20% of patients) and there is limited benefit in BRAF mutant colorectal carcinoma.

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Profile of preclinical candidates

Recent developments in understanding the biological effects of BRAF kinase inhibitors suggest that the preferred product profile would be a potent BRAF inhibitor that also inhibits CRAF protein kinase in order to prevent pathway activation in cells mutant for RAS (Heidorn et al. *Cell* 2010;140(2):209–21). Inhibiting CRAF is believed to be beneficial in preventing the onset of squamous cell carcinoma, which is observed as a side-effect with vemurafenib, the current treatment (Su et al. *NEJM* 2012;366(3):207–15).

Both preclinical candidates are potent (nanomolar) inhibitors of mutant BRAF with the following characteristics:

Potency and selectivity

- Low nM activity against BRAF, CRAF and pERK and in SRB assays.
- Broader selectivity profile than reported for vemurafenib by inhibiting CRAF.
- Type II kinase inhibitors in contrast to vemurafenib (type I).

DMPK

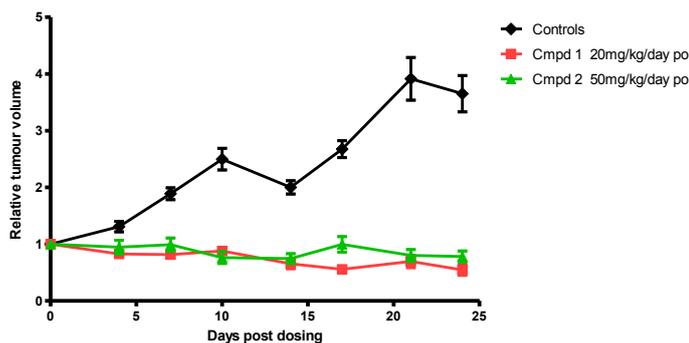
- Good oral bioavailability with long plasma half-lives *in vivo*.
- Low mouse and human *in vitro* metabolism.
- Low cytochrome P450 inhibition.

Safety and toxicity

- Do not inhibit hERG.

In vivo efficacy

The preclinical candidates exhibit good oral bioavailability and inhibit tumour growth in mutant BRAF-driven melanoma (see figure 1) and colorectal xenograft models and in mutant RAS-driven xenograft models (data available upon request).



Oral therapeutic efficacy of selected candidate compounds in BRAF-driven melanoma

Preclinical and clinical development

The preclinical development strategy is in line with ICH S9 guidelines. The candidates will be nominated as lead and backup respectively in Q2 2012. The clinical trial will be a single-centre, open-label study of a candidate drug in patients with advanced melanoma. The study will be conducted in two parts: phase Ia, dose escalation (20 patients); and phase Ib, melanoma specific expansion (up to 74 patients). In the expansion phase of the study, the patients will be recruited into three clinically and molecularly defined groups. Thus, the results will indicate the potential benefits compared with vemurafenib in mutant BRAF and mutant RAS driven tumour types.

Team

The preclinical candidates were developed in the laboratories of Professor Richard Marais and Professor Caroline Springer at the Institute of Cancer Research (ICR). The adaptive and expansion phase I trial will be performed by melanoma experts Professor Martin Gore and Dr James Larkin at the Royal Marsden. The ICR in partnership with the Royal Marsden is at the forefront of cancer research and has a drug discovery facility on site. Many drugs discovered or developed at the ICR have successfully entered the clinic and market. Additionally, the Royal Marsden, together with the ICR, is designated the UK's only NIHR Biomedical Research Centre for Cancer.

Intellectual property

There is a robust patent portfolio protecting the lead series and surrounding chemical space, with both composition of matter and medical use claims to the key compounds.

Commercial partnership

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MC-5013.7/25/1-2012/BS